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Synthesis of Ynone Trifluoroborates toward Functionalized Pyrazoles

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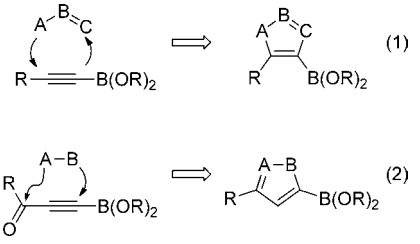
ABSTRACT

The synthesis of a range of novel ynone trifluoroborates has been achieved, in a two-pot process from propargylic alcohols. These alkynes have been subsequently used in the formation of a range of pyrazole trifluoroborate salts *via* cyclization with hydrazines. The products are generated with high levels of regiocontrol and in excellent yields and represent versatile synthetic intermediates.

Heteroaromatic compounds play a pivotal role in all aspects of the chemical sciences and are found as core motifs in a wide range of compounds from ligands in coordination complexes to biologically active molecules and building blocks used in smart materials.[1] Accordingly, a range of techniques have been developed for the ring synthesis of functionalized heteroaromatic compounds. Among the many methods now available, those that endow the heteroaromatic products with a readily elaborated functional group are of particular interest, as they offer the potential to incorporate these motifs into a range of new chemical frameworks. In this context, previous studies within our group have demonstrated that a wide range of aromatic and heteroaromatic boronic acid derivatives can be synthesized via cycloaddition reactions of alkynylboronates (Scheme 1, eq 1).[2] This chemistry exploits the compatibility of the alkyne with a range of dienes and 1,3-dipolar intermediates, as well as metal catalyzed benzannulation techniques. However, a strategically different but equally versatile employment of alkynes in heterocycle synthesis involves the addition of a nucleophile across an ynone.[3] To the best of our knowledge, such a transformation has not been reported to date using borylated alkynes. We therefore wanted to develop a robust route to a range of ynone boronic acid derivatives and to explore the participation of these compounds in the formation of functionalized heteroaromatic scaffolds (Scheme 1, eq 2). We report our results toward this goal herein.

Scheme 1. Proposed Route to Aromatic Boronic Esters



Our first task was to devise a practical route toward the requisite alkynylboronate intermediates. These compounds have received only scant attention in the literature, and while

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(1) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Publishing: 2001. (b) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943. (c) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984.

(2) (a) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707. (b) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889. (c) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860. (d) Delaney, P. M.; Moore, J. E.; Harrity, J. P. A. *Chem. Commun.* **2006**, 3323. (e) Browne, D. L.; Vivat, J. F.; Plant, A.; Gomez-Bengoa, E.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2009**, *131*, 7762. (f) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2009**, 436. (g) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866. (h) Vivat, J. F.; Adams, H.; Harrity, J. P. A. *Org. Lett.* **2010**, *12*, 160. (i) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2012**, 6402.

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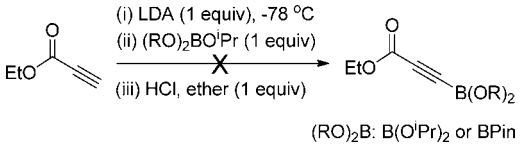
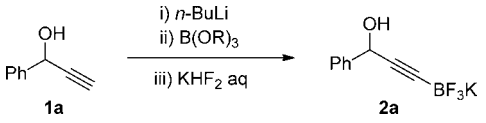
a selection of alkynyl diamidoboranes are known,[4] only a single example of a propiolate derived alkynylboronate has been reported.[5] Indeed, our attempts to prepare analogous propiolate-based alkynylboronates failed, and despite significant efforts to optimize this procedure we were unable to isolate any target material using this method (Scheme 2).

Scheme 2. Attempted Syntheses of Propiolate Boronates



Given the difficulties observed in isolating the key electron-deficient alkynylboronates, we opted to explore the corresponding trifluoroborates. These compounds are widely acknowledged to exhibit enhanced stability in comparison to the corresponding boronic acid derivatives.[6] While ynone trifluoroborates had not been documented in the literature, we were encouraged by a recent report by Evano which demonstrated the direct synthesis of a *propargyl alcohol* trifluoroborate from the corresponding propargylic alcohol.[7] This offered the intriguing possibility of carrying out direct conversion of the borate-substituted propargyl alcohols to the target ketones by taking advantage of the functional group tolerance of trifluoroborates toward oxidation.[8]

Table 1. Optimization of a Trifluoroborate Synthesis[a]

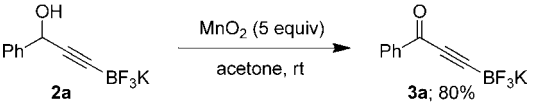


entry	method	$B(OR)_3$	yield **2a**/%
1	A	$B(OMe)_3$	22
2	B	$B(OMe)_3$	56
3	B	$B(O^iPr)_3$	43
4	B	^{i}PrOBPin	92

[a] Method A: BuLi (1.1 equiv), $B(OR)_3$ (1.5 equiv), KHF_2 (6.0 equiv). Method B: BuLi (2.2 equiv), $B(OR)_3$ (3.0 equiv), KHF_2 (12.0 equiv).

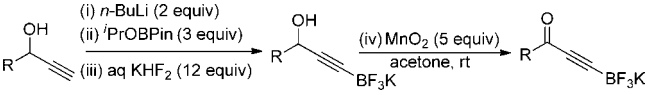
In the event, we were able to employ Evano's method successfully to form the trifluoroborate salt of 1-phenyl propargyl alcohol, albeit in low yield. Further optimization of the reaction stoichiometry and boronate ester source highlighted that this process could be significantly improved, providing a convenient means for preparing **2a** in high yield (Table 1). Moreover, on turning our attention to the key oxidation step, we were delighted to find that manganese dioxide smoothly delivered the desired ynone **3a** in high yield (Scheme 3).

Scheme 3. Synthesis of an Ynone Trifluoroborate



As stated earlier, alkynylborane derivatives bearing electron-deficient groups are rather rare, so we opted to explore the scope of this protocol for the synthesis of a range of these compounds, and our results are summarized in Table 2. We were pleased to find that the products can be formed on multigram scale, although in slightly reduced yield (Table 2, entry 2). The method was also effective for electron-rich aryl-substituted propargyl alcohols (Table 2, entries 3 and 4). Notably, the oxidation is not restricted to aryl-substituted propargyl alcohols. Oxidation of aliphatic substituted compounds **2e**–**2g** took place smoothly to provide the corresponding products in acceptable overall yields (Table 2, entries 6–8).

Table 2. Synthesis of Ynone Trifluoroborate Salts



entry	R	yield (i)–(iii)/%	yield (iv)/%	overall yield/%
1	Ph; **1a**	**2a**; 92	**3a**; 80	74
2[a]	Ph; **1a**	**2a**; 81	**3a**; 61	49
3	*p*-$MeOC_6H_4$; **1b**	**2b**; 42	**3b**; 78	33
4	*o*-$MeOC_6H_4$; **1c**	**2c**; 62	**3c**; 83	51
5	*p*-$F_3CC_6H_4$; **1d**	**2d**; 48	**3d**; 93	45
6	Me; **1e**	**2e**; 48	**3e**; 60	29
7	*n*-Pr; **1f**	**2f**; 80	**3f**; 81	65
8	*t*-Bu; **1g**	**2g**; 63	**3g**; 91	57

[a] Reaction performed on 5 g scale.

Having successfully achieved the synthesis of a library of ynone trifluoroborates, attention was turned to their use as precursors to heteroaromatic trifluoroborates. We decided to investigate the addition of highly nucleophilic hydrazines

(3) (a) Birkofer, L.; Hänsel, E.; Steigel, A. *Chem. Ber.* **1982**, *115*, 2574. (b) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1320. (c) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem.* **1993**, *30*, 755. (d) Adlington, R. M.; Baldwin, J. E.; Catterick, D. E.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 855. (e) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523. (f) Bagley, M. C.; Hughes, D. D.; Taylor, P. H. *Synlett* **2003**, 259.

(4) (a) Lhermitte, F.; Carboni, B. *Synlett* **1996**, 377. (b) Blanchard, C.; Vaultier, M.; Mortier, J. *Tetrahedron Lett.* **1997**, *51*, 8863.

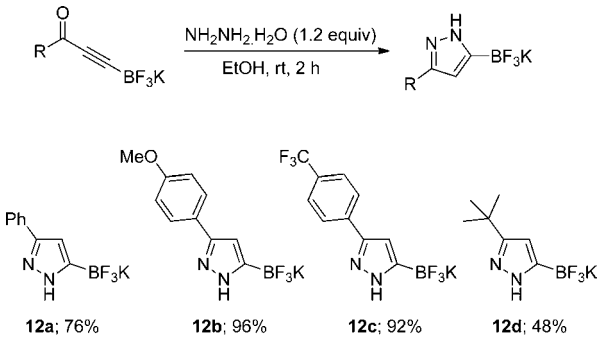
(5) Morita, R.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Org. Biomol. Chem.* **2005**, *3*, 1263.

(6) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240.

(7) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272.

(8) Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634.

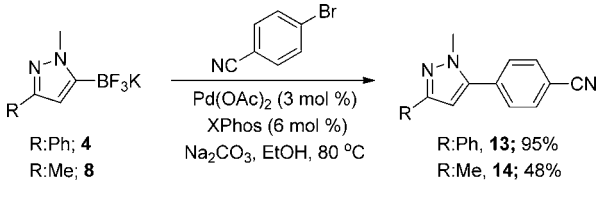
Scheme 4. Synthesis of *N*-H Pyrazole Trifluoroborates



to our borylated ynones, as this would provide a convenient means for preparing pyrazole scaffolds which are of interest as intermediates within the fine chemicals sector.[1c] As outlined in Table 3, simply stirring a mixture of aromatic ynones **3a**–**3d** with methylhydrazine in ethanol at room temperature delivered the corresponding functionalized pyrazole trifluoroborates in excellent yields and regioselectivities within 4 h (Table 3, entries 1–4). Moreover, the method could be extended to include the corresponding alkyl substituted ynones **3e**–**3g** (Table 3, entries 5–7).[9] Interestingly, use of phenyl hydrazine reverses the reaction regioselectivity, providing 3-borylated pyrazole **11b** (Table 3, entry 8). This result mirrors the observations made by Bishop, who proposed that reaction regioselectivity arises from conjugate addition of the most nucleophilic hydrazine nitrogen atom on the enyne.[10]

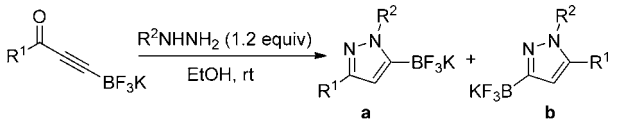
The results outlined in Table 3 highlight the flexibility of this technique for the synthesis of a range of 1,3,5-trisubstituted pyrazoles; however, we recognized that performing the reaction with hydrazine could offer a direct method for generating these analogues with a free amino group. As outlined in Scheme 4, we were pleased to find that this method is very well suited to the synthesis of these particular compounds, and the appropriate pyrazoles were obtained in acceptable yields in all cases.

Scheme 5. Cross-Coupling of Pyrazole Trifluoroborates



To demonstrate the utility of the pyrazole trifluoroborates, a number of further functionalizations were performed. Pleasingly, we found that the cross-coupling of both pyrazoles **4** and **8** could be achieved successfully utilizing conditions previously reported by Molander, affording coupled products **13** and **14** in excellent and moderate yield, respectively (Scheme 5).[11]

Table 3. Synthesis of Pyrazole Trifluoroborate Salts

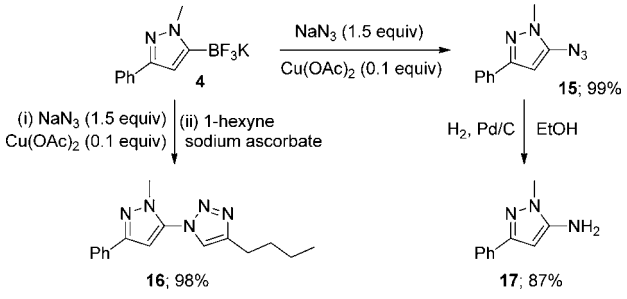


entry	R^1	R^2	time/h	yield/%	ratio **a**:**b**
1	Ph	Me	4	**4**; 96	16:1
2	*p*-$MeOC_6H_4$	Me	2	**5**; 63	7:1
3	*o*-$MeOC_6H_4$	Me	3	**6**; 92	>98:2
4	*p*-$F_3CC_6H_4$	Me	0.5	**7**; 98	>98:2
5[a]	Me	Me	18	**8**; 74	9:1
6[a]	*n*-Pr	Me	18	**9**; 78	15:1
7	*t*-Bu	Me	16	**10**; 92	>98:2
8[a]	Ph	Ph	19	**11**; 88	<2:98

[a] Reactions heated at 40 °C.

We were also pleased to find that the azidonation of pyrazole **4** could be achieved smoothly (Scheme 6). Utilizing conditions previously reported by Aldrich, azidonated pyrazole **15** formed in excellent yield.[12] A one-pot azidonation–click reaction was also successful, providing pyrazole-triazole product **16** in excellent yield, as a single regioisomer. Reduction of azido-pyrazole **15** was also achieved, affording amino-pyrazole **17** in high yield.[13]

Scheme 6. C–N Functionalization of Pyrazole Trifluoroborates



In conclusion, we have demonstrated a novel route to substituted pyrazole trifluoroborates via the cyclization

(9) To determine the reaction regioselectivity, pyrazoles **4**, **6**, **8**, **9**, and **11** were subjected to a base-mediated deborylation, affording a previously reported 1,3- or 1,5-substituted pyrazole as the major product in each case (see Supporting Information for details).

(10) Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43.

(11) (a) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973. (b) Molander, G. A.; Argintaru, O. A.; Aron, I.; Dreher, S. D. *Org. Lett.* **2010**, *12*, 5783.

(12) Grimes, K. D.; Gupte, A.; Aldrich, C. C. *Synthesis* **2010**, 1441.

(13) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2010**, *75*, 984.

reaction of ynone trifluoroborates with hydrazines. Utilizing this method, a range of pyrazole trifluoroborates has been synthesized under mild conditions, in excellent yields and regioselectivities. The resulting products undergo C−C and C−N bond forming reactions giving rise to a series of functionalized pyrazole scaffolds. We hope that, in the future, we can demonstrate the use of ynone trifluoroborates as precursors to a range of alternative borylated heteroaromatics.

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Supporting Information Available. Full experimental details and characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.